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CARBOPLATIN-BASED COMBINATION CHEMOTHERAPY FOR TESTICULAR CANCER: RELATIONSHIP AMONG ADMINISTRATION DOSE OF CARBOPLATIN, RENAL FUNCTION AND MYELOSUPPRESSION

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Carboplatin (CBDCA), a derivative of cis-diamminedichloroplatinum, has low renal and neural toxicity. The dose-limiting factor of this agent is myelosuppression. We experienced various degrees of myelosuppression, when the dose of CBDCA was determined by the body surface area (BSA) in CBDCA-based combination chemotherapy for testicular cancer. Calvert demonstrated that the dose of CBDCA administered should be adjusted by renal function, because CBDCA was excreted through the glomerulus. We report the relationship among 3 factors; the administration dose of CBDCA, renal function and the degree of myelosuppression.

We treated 6 patients with testicular cancer. A total of 22 courses of CBDCA-based combination chemotherapy was performed. The area under the curve (AUC) was calculated by the following formula, which was demonstrated in Calvert's study.
CBDCA dose=AUC×(GFR+25), GFR; glomerular filtration rate. The degree of myelosuppression was examined. All chemotherapy courses were divided into 2 and 3 groups according to BSA and AUC, respectively. WBC and Plt reduction rates and nadir counts were significantly correlated with AUC, and showed no significant relationship to the dose determined by BSA. This study revealed that the degree of myelosuppression was closely related with AUC, which reflects the renal function.

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Key words: Carboplatin, Renal function, Myelosuppression

INTRODUCTION

Testicular cancer, even with metastasis, is a curative cancer for the excellent sensitivity for the anti-cancer agents. Of these agents, cis-diamminedichloroplatinum (CDDP) has a high anti-tumor effect and is an essential agent for testicular cancer. Standard regimens, which are chosen for the first line chemotherapy, i.e., PVB[1], VAB-6[2] or PEB[3] therapy, contain CDDP. Recent trends in chemotherapy for testicular cancer demonstrated the minimum invasive treatment for the low-risk group[4] and the intensive treatment for the poor-risk group[5,6]. Alternative agents are selected, which have low adverse effects and have an anti-tumor effect to the same degree. For example, omission of bleomycin has been tried for the possibility of lung toxicity[4]. As for CDDP, renal toxicity is a major and well-known adverse effect[7]. Testicular cancer predominantly affects the younger generation, with good renal function. Therefore, in most cases, the full dose of CDDP could be administered according to the regimen. However, attention must be paid to the renal function after CDDP administration in some cases. Reduced contralateral

renal function by the metastatic mass involving the renal hilum; rather high-age cases with advanced seminoma with incidence in older generations compared with non-seminomatous germ cell tumor, will be a disadvantage for chemotherapy. Furthermore, peripheral neuropa- thy is a troublesome complication of CDDP[8,9] and worsens the quality of life of the patients.

Recently, carboplatin (CBDCA), which is a derivative agent of CDDP, has been available. The characteristics of this agent lies in low nephro- and neural- toxicities and the dose-limiting factor is myelosuppression, which is mild or moderate in the case of CDDP. CBDCA had been administered at 300~400 mg/m^2 as a single agent or at 3 or 4 times dose of CDDP as a combination chemotherapy[10]. From our experience of CBDCA- based combination chemotherapy, the degree of myelosuppression was various among cases, when CBDCA was administered at a dose determined by the body surface area as mentioned above. In some studies[11], the relationship between the degree of myelosuppresion and the renal function has been examined. CBDCA is excreted through the glomerulus and the serum CBDCA concentration is varied by the glomerular filtration rate (GFR). This varied serum level brings a varied degree of myelosuppression. On the basis of these phenomena, Calvert et al proposed that CBDCA should be administered at a dose adjusted by GFR[12,13].

In this study, we examined the relationship among the administration dose of CBDCA, renal function and the degree of myelosuppression in the CBDCA- based combination chemotherapy for testicular cancer.

PATIENTS AND METHODS

Six patients with histologically proven testicular cancer were treated with CBDCA-based combination chemotherapy at the Gunma University Hospital and the related hospitals between March, 1993 and April, 1994. Table 1 shows the details of the patients characteristics. Two patients had stage I seminoma with elevated human chorionic gonadotropin beta-subunit at the first presentation, 1 had stage IIA seminoma, and the other 3 had stage IIA non seminomatous germ cell tumor. CBDCA was administered as CVB therapy (CBDCA 80 mg/m^2; day 1~5, vinblastine 0.3 mg/kg; day 1, bleomycin 30 mg; day 2, 9, 16) and as CE therapy (CBDCA 80~33.3 mg/m^2; day 1~5, etoposide 100 mg/m^2). Patient No-4 treated with CVB therapy had recurrence 6 months after the induction therapy and was treated with CE therapy. Patient No-3 was firstly treated with PEB therapy and his renal function was reduced by the first course therapy. Then, the second and third courses were treated with CE therapy. Therefore, CBDCA- based combination chemotherapy was performed as 9 courses of CVB therapy in 3 patients and as 13 courses of CE therapy in 4 patients.

Renal function was evaluated before each treatment course by 24-hour creatinine clearance (Ccr) and with reference to the separate measurements of 24-hour Ccr was mean level of 2 referred. The degree of myelosuppression was evaluated by the nadir count and the reduction rates of white blood cell (WBC) and platelet (Plt). The reduction rate was defined as the ratio of the reduced cell count to the pretreatment cell count. As a parameter of the renal function and the CBCDA dose, AUC (area under the curve) was calculated with the following formula proposed by Calvert *et al.*

$$\text{AUC (mg/ml} \times \text{min)} = \text{CBDCA dose (mg)} / (\text{GFR} + 25)$$

GFR was approximated to Ccr. AUC was retrospectively calculated from CBDCA dose and GFR.

The recombinant granulocyte colony stimulating factor was administered to Patient-No-3 at the recovery phase from WBC nadir point.

Data were analyzed by Student's- t test or Mann- Whitney- U test and were considered as significant when p values were less than 0.05.

RESULTS

Table 2 shows the reduction rates and

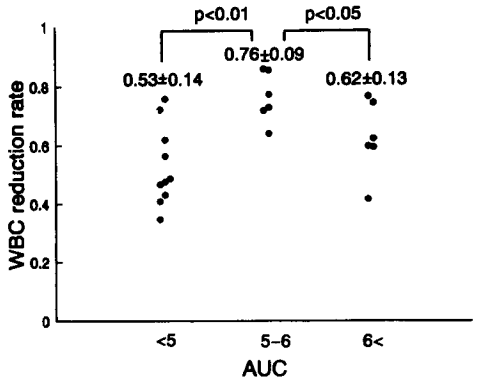

Fig. 1. The relationship between WBC reduction rate and AUC.

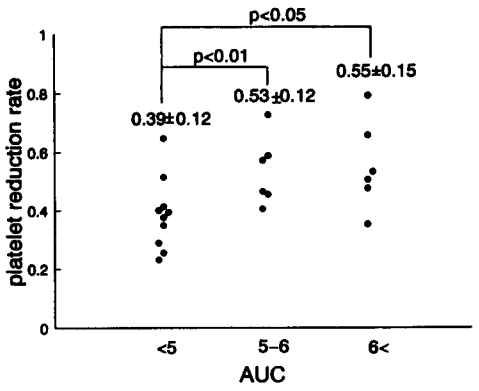

Fig. 3. The relationship between Plt reduction rate and AUC (all courses).

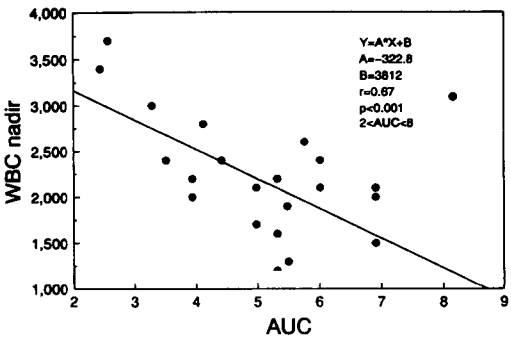

Fig. 2. The relationship between WBC nadir count and AUC.

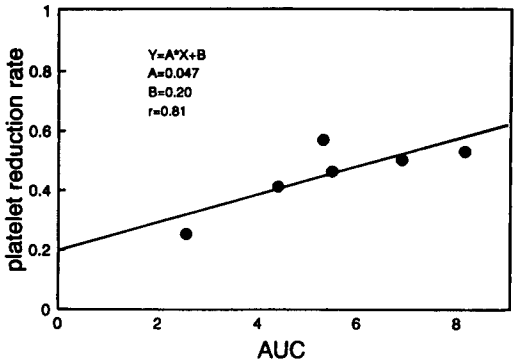

Fig. 4. The relationship between Plt reduction rate and AUC (first course).

the nadir counts of WBC and Plt after administration of CBDCA according to the body surface area. When all the treatment courses were divided into 2 groups, 60 mg/m² or less group and 80 mg/m² group, the changes of WBC and Plt showed no significant differences between the two groups.

Then, all courses were divided into 3 groups according to AUC; group A: less than 5, group B: 5≦ and ≦6, group C: more than 6. WBC reduction rates in group A and C were significantly lower than in group B (Fig. 1). Nadir WBC count showed a significant decrease according to the AUC elevation (Fig. 2). The Plt reduction rate in group A was

Table 1. Patients characteristics

Patient No.	Age	Stage	Pathology	Regimen	Treatment courses	Ccr (ml/min)	Response	Recurrence	Current status
1	34	I	S	CE	3	112.3-134.8	—	—	NED (+1y 3Mo)
2	63	I	AS	CE	3	69.0	—	—	NED (+2y Mo)
3	34	IIA	S	CE	2	47.8- 74.7	CR	—	NED (+9Mo)
4	26	IIA	TC	CVB	3	83.5	CR with RPLND	—	NED (+3y 8Mo)
5	36	IIA	T	CVB	3	102.1-119.0	CR with RPLND	6Mo	alive with tumor (+10Mo)
6-a	21	IIA	E	CVB	3	66.9- 99.7	CR	6Mo	—
6-b	22	IIIC	E	CE	5	105.2-125.6	PD	—	death (13Mo)

S: seminoma with elevated HCG-β, AS: anaplastic semimona, E: embryonal carcinoma, TC: teratocarcinoma, T: teratoma. CE: CBDCA+etoposide, CVB: CBDCA+VLB+BLM. RPLND: retroperitoneal lymph node dissection. NED: no evidence of disease, Ccr: creatinine clearance. *: Patient No 6-b was recurrent status of Patient No 6-a with lung and brain metastasis.

Table 2. The change of platelet and WBC count after administration of CBDCA according to the body surface area

	CBDCA dose	60 mg/m^2≧	80 mg/m^2
Platlet	Reduction rate	0.45±0.17	0.48±0.14
	Nadir (×10,000)	11.9 ±3.0	14.9 ±3.9
WBC	Reduction rate	0.57±0.19	0.64±0.13
	Nadir	2,537.5±860.1	2,100±452.3

values are shown as mean±SE.

significantly lower than both in group B and C, and that in group C was significantly higher than that in group B (Fig. 3). Plt reduction rates in the first course (6 courses) were plotted in Fig. 4. The rates were highly correlated with AUC.

Table 1 shows the response and current status of the patients. Two patients with stage I seminoma have no recurrence. Other 4 patients had a complete response with or without retroperitoneal lymph node dissection. Patients No-3 and No-4 had no evidence of disease. Patient No-5 hiad recurrence at retroperitoneal, mediastnal and cervical lymph nodes with mature teratoma. This patient is now under treatment. Patient No-6 had recurrence at lung and brain 6 months after the first induction therapy and died 13 months after the recurrence.

DISCUSSION

The effect of anti-cancer agents on the bone marrow function is regulated by administration dose, other combined agents, patient age, the kinds of prior therapy and so on. CDDP is administered at a dose of 20 mg/m^2 for 5 consecutive days in PVB and PEB therapies, and has a reliable anti-tumor effect with vinblastine or etoposide. Furthermore, the degree of myelosuppression may be estimated. In the case of substitution of CBDCA for CDDP, the following prerequisite will have to be satisfied; the degree of myelosuppression by CBDCA is manageable as in PVB or PEB therapy and is possible to be preestimated. Because the dose-limiting factor of CBDCA is thought to be the myelosuppression. This study, although it was small, demonstrated that the administration dose should be determined not by the reference of the body surface area but by the reference of AUC, which reflected the renal function as proposed by Calvert at al[12,13].

The CBDCA molecule is rather stable in plasma[14,15]. The majority of the molecule remains as an intact drug over the initial 4 to 6 hours[16,17]. The decay curves for the intact CBDCA and free platinum are considered almost identical and are fitted to an mono-exponential curve[18–20]. Although the longer beta-phase half-lives were detected, they did not affect AUC for their low plasma concentrations[13]. CBDCA is excreted exclusively by glomerular filtration tr little tubular contribution.[14] However, non-renal excretion exists, which is dependent on body size[12 13]. These factors are explained by the one-compartment model, in which renal clearance depending upon GFR and non-renal clearance equilibrate to compartmental body with some plasma CBDCA level[13]. Carvert *te al.*[12,13] demonstrated the above mentioned formula considering these characteristics of CBDCA.

As for Plt reduction rate, group C had a significantly high reduction rate of 0.55 as a mean. On the other hand, group B had a significantly higher WBC reduction rate. Group B had a 63-year-old patient with stage I seminoma and this patient had about an 0.8 reduction rate in all 3 courses. Considering the age of other patients, the value of this patients had the possibility of modifying the data of group B. When excluding these data, reduction rate was 0.73±0.11 (mean±S.E.). This value was significantly higher than that in group A, but was not significantly different from that in group C.

AUC is a pharmacokinetic parameter; it shows the area under the serum concentration curve against the time after the administration. Calvert et al[12] reported that the difference between the actual AUC and the AUC calculated from the above mentioned formula was less than 10%. Newell et al[21] analyzed the pharmacokinetics of CBDCA and etoposide in

testicular cancer chemotherapy and reported the efficacy of Calvert's formula.

AUC in this study ranged from 2.4 to 8.1. This suggested that in some patients, the AUC was below the treatment level. On the other hand, Plt transfusion was not necessary even in group C. There were no patients whose WBC nadir counts were less than 1000. In PVB or PEB therapy, the WBC nadir count was frequently less than 1000, and Plt transfusion was sometimes required. These findings, suggest that we can manage to support the myelosuppression with conventional modalities in the case whose AUC is from 5 to 7. Horwich et al[22] demonstrated that the first course of CEB therapy should be started at a dose determined by AUC 4.6~5 and that the dose of further courses should be adjusted by the degree of myelosuppression by the first course. The CBDCA dose determined by AUC 5 in a combination chemotherapy was indicated as a dose for a Plt reduction rate. of 70% We support this method of dose determination; the first course should be started with AUC about 5, a safe dose.

We retrospectively analyzed CBDCA-based combination chemotherapy, particularly regarding myelosuppression and AUC. AUC is useful in determining the optimal administration dose of CBDCA. We chose AUC 5 as the dose of the first course. We can regulate the dose of the next course by GFR and AUC. A safe and effective treatment will be possible considering these facts. Furthermore, these concepts will be applicable to other drugs which are mainly excreted from glomerulus.

In summary, myelosuppression after CBDCA- based combination chemotherapy was regulated by the dose determined by AUC rather than the dose determined by the body surface area. The concept regarding AUC was efficacious for the safe and effective CBDCA dose determination. We will further examine the clinical course of CBDCA- based combination chemotherapy.

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和文抄録

精巣腫瘍におけるカルボプラチンを含む多剤併用化学療法：投与量，腎機能と骨髄抑制について

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カルボプラチンはシスプラチンの誘導体であり腎毒性および神経毒性が低い．投与量規定因子は骨髄抑制である．われわれは数人の精巣腫瘍患者にたいし，カルボプラチンを基本とした多剤併用療法を施行した．カルボプラチンの投与量は体表面積で調整した．骨髄抑制の程度が各コースによりたいへん異なっていた．カルバートによる最近の報告ではカルボプラチンは腎機能により調節した投与量で投与すべきということを示した．われわれはこの研究で，カルボプラチン投与量，腎機能と骨髄抑制の関係を検討した．

6例の精巣腫瘍患者にたいし計22コースのカルボプラチンを基本とした多剤併用療法を施行した．AUC，曲線下面積は，カルバートにより示された以下の公式により算出した．カルボプラチン投与量＝AUC ×（GFR＋25）GFR；糸球体ろ過率．骨髄抑制の程度をいくつかのカテゴリーにより検討した．化学療法のコースを体表面積あたり投与量により2群にわけた．白血球および血小板の減少率，最低値はこの2群の間で有意差を認めなかった．一方，AUC により3群に分けた場合，AUC の高い群は骨髄抑制の程度が高かった．今回の検討より骨髄抑制の程度は腎機能を反映している AUC により影響を受けることが示された．

（泌尿紀要 41：775-780，1995）